Image RCE/17/14

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Request For Continued Examination (RCE) Transmittal

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Application Number	10/087,140
Filing Date	February 27, 2002
First Named Inventor	Panattoni, Cory M.
Art Unit	1714
Examiner Name	Yoon, Tae H.
Attorney Docket Number	002558-067300US

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
      ii. ☐ Other _____

   b. ☐ Enclosed
      i. ☒ Amendment/Reply
      ii. ☐ Affidavit(s)/ Declaration(s)
      iii ☒ Information Disclosure Statement (IDS)
      iv. ☐ Other _____

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) **required**)

   b. ☐ Other _____

3. **Fees** The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. ☒ The Director is hereby authorized to charge the following fees, or credit any overpayments, to Deposit Account No. 20-1430
      i. ☒ RCE fee required under 37 CFR 1.17(e)
      ii. ☒ One (1) Extension of time fee (37 CFR 1.136 and 1.17)
      iii. ☐ Other _____

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Name (Print /Type)	Joel G. Ackerman	*Registration No. (Attorney/Agent)*	24,307
Signature		*Date*	February 27, 2004

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On **February 27, 2004**

TOWNSEND and TOWNSEND and CREW LLP

By: _____
Lois M. Simón

PATENT
Docket No.: 002558-067300US
Client Ref. No.: BRP00324

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Examiner: Yoon, Tae H.
CORY PANATTONI	Art Unit: 1714
Application No.: 10/087,140	REQUEST FOR CONTINUED EXAMINATION
Filed: February 27, 2002	
For: PREPARATION OF DEFECT-FREE POLYACRYLAMIDE ELECTROPHORESIS GELS IN PLASTIC CASSETTES	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the office Action (Final Rejection) dated October 17, 2003, Applicant hereby requests continued examination of this application, taking into account the comments herein and the material submitted by the accompanying Information Disclosure Statement. An extension of time for filing the Appeal Brief has been requested.

The invention claimed in this application is a process for casting a polyacrylamide gel that enables such a gel to be cast in a plastic gel enclosure, e.g.,

between plastic plates. As pointed out in the specification, there is a problem associated with the use of plastic plates or enclosures for such gels, namely that oxygen - which may be present in the plastic or which may seep though it (as air) - causes irregularities in the gel pore size near the gel/plastic interface, which in turn produce a distortion of the solute bands in the gel. As discussed in earlier communications, such problems do not occur when casting gels between glass plates since glass is impermeable to gases.

Applicant's solution to this problem is the incorporation in the gel casting mixture (including an acrylamide and a cross-linking agent) of an oxygen scavenger selected from the group consisting of sodium sulfite, sodium bisulfite, sodium thiosulfate, sodium lignosulfate, ammonium bisulfite, hydroquinone, diethylhydroxyethanol, diethylhydroxylamine, methylethylketoxime, ascorbic acid, erythorbic acid, and sodium erythorbate. This makes it possible to take advantage of the benefits of using plastic plates or other enclosures while at the same time being able to provide a gel that functions with similar accuracy to one enclosed within glass plates. With one exception, the cited prior art is clueless as to how to accomplish this, and the exception uses a totally different technique.

The claims in this applications stand variously rejected as obvious over combinations of several references. However, as discussed below, Applicant submits that the combinations of references either are not appropriate or do not result in the claimed invention.

Claims 1-3 and 6-0 stand rejected as obvious over the combination of Hochstrasser et al. with Alpenfels et al. or Lau et al.

Hochstrasser et al. disclose a process for gel formation in which the gel is to be used as a matrix in a process for detection of biological material by silver staining. The focus in this reference is on the reduction of background staining. According to the Hochstrasser et al invention, sodium thiosulfate was found suitable for this purpose, and is therefore included in the gel formation process. Thiosulfate is known in the electrophoresis art for its ability to sensitize proteins so that they will more strongly bind to silver and thereby increase the sensitivity of the stain, and also for its ability to form

complexes with silver, thereby preventing the precipitation of silver carbonate (which causes background staining). However, there is no suggestion in Hochstrasser et al. or elsewhere that thiosulfate could also reduce the occurrence of irregularities at the interface between a gel and a plastic enclosure.

Background staining occurs in the bulk of the gel after the gel has been removed from the enclosure and stained, while interfacial irregularities occur at the interface between the gel and the enclosure while the gel is being cast. One would not readily suspect that an additive such as thiosulfate that is known only to serve its function in the bulk of the gel would be effective in correcting problems that arise only at the gel-enclosure interface.

The examiner takes the position that Hochstrasser et al. teach the present composition (and presumably the present process). However, such a position does not take into account the Hochstrasser et al. disclosure as a whole, as is required by 35 USC 103. Hochstrasser et al. sought to deal with a specific problem in the prior art, namely reduction or elimination of undesirable background staining. In their work, these inventors tried a number of compounds for this purpose, but found that only one - sodium thiosulfate - accomplished it. On the other hand, Hochstrasser et al. tried other compounds within the scope of the present claims, and found that they were detrimental to their process. The reference states (col. 12 lines 43-67):

"Since *no further reductions in background staining could be achieved beyond that observed with DMPIP or TEMED, different salts were tested either to replace the organic bases and to be added to the persulfate or even to replace the persulfate. None of the salts tested (see FIG. 2) produced adequate polymerization if used alone. Only ammonium or potassium persulfate used with another compound produced good polymerization and their effect on the background staining was identical (FIG. 2, #14-17). However, the addition of different anions dramatically modified the background stain from a yellow stain for sulfate to a dark brown stain for permanganate. ...*

The addition of sodium sulfite accelerated the polymerization process, and gels were polymerized with APS and sulfite without organic base. However, sulfite

increased the background staining more than TEMED or DMPIP. None of the other salts tested could replace the organic base. The addition of thiosulfate slowed down the polymerization, but it totally eliminated the appearance of any background during prolonged development times with cooled developer solution, despite the use of persulfate and TEMED or DMPIP (FIG. 2, #21)."

Thus, sodium sulfite was found unsuitable for use in the Hochstrasser et al. process. Similarly unsuitable were sodium bisulfite, sodium hydrosulfite, potassium metabisulfite, sodium sulfate, and others (col. 10 lines 25-68; table bridging cols. 13 and 14).

Hochstrasser et al. thus contains teachings that incline both towards and contrary to the claimed invention. That is, Hochstrasser et al. teach that sodium thiosulfate should be incorporated in the gel formation process, and that sodium sulfite and bisulfite (both claimed for Applicant's process) should not be incorporated. It is inappropriate for the examiner to rely only on information that supports one point of view while not taking into account information that directs those skilled in the art to not use compounds claimed by Applicant. In addition, those skilled in the art would obtain no information from Hochstrasser et al. on solving the problems caused by oxygen at the surface of the gel.

Applicant notes that the examiner implicitly recognized these contrary teachings inasmuch as claims 4 and 5 are not rejected over this combination of references.

The overall Hochstrasser et al. disclosure does not render Applicant's claimed process obvious, whether alone or in combination with the secondary references.

Hochstrasser et al. ran their process in glass plates only. The examiner cites Alpenfels et al. and Lau et al. for the proposition that advantages of plastic plates are known and that it would be obvious to run the Hochstrasser et al. process in plastic plates. Applicant agrees that plastic and glass plates were known at the time his invention was made. However, as mentioned, Hochstrasser et al. does not, and did not need to, deal

with the problems of oxygen contact with the gel that are encountered when using plastic plates.

Alpenfels et al., on the other hand, were aware that oxygen diffusion into the gel should be prevented (though the nature of the problem caused is not mentioned in this reference). They dealt with this by using plastic films that had a special coating that provided an oxygen barrier. This is described in Alpenfels et al. at col. 5 lines 30-45. In fact the Alpenfels et al. disclosure is directed to the use of plastic films on a certain framework. The use of plastic plates or films having an oxygen barrier obviates the need for use of Applicant's oxygen scavengers. On the other hand, the use of Applicant's oxygen scavengers removes the need for an oxygen barrier, which can decrease the production cost.

Thus, those skilled in the art would not find it obvious to combine the Hochstrasser et al. process with that of Alpenfels et al. in order to avoid the problems associated with the presence of oxygen since the latter already provides a means for dealing with that. Additionally, those skilled in the art would be taught away from using certain of the claimed salts by Hochstrasser et al. Finally, any combination of the two references would result in the Hochstrasser et al. process being carried out using the Alpenfels specially constructed plastic films with oxygen barriers, whereas Applicant's invention obviates the need for such barriers. Indeed, in Applicant's process such barriers would be superfluous.

Lau et al. deal with aspects of the construction of a system of plates for use in gel production. In passing they mention (col. 4 lines 38-43) that the system could include either glass or plastic plates. The reference discloses nothing further about plastic plates. It does not disclose whether or not their plastic plates present any problem with oxygen contact at the gel surface. In the absence of any information to the contrary, one can only assume that if Lau et al. were in fact to use plastic plates in a construction, they would be provided with an oxygen barrier as disclosed in Alpenfels et al. to avoid this problem.

Applicant's claimed process provides cross-linked polyacrylamide gels of good quality contained within plastic plates or other enclosures. The prior art (except possibly for Alpenfels et al.) simply does not provide such a product, nor does it render it obvious how such a product may be obtained.

For the above reasons, the rejection of claims as obvious over the proposed combination of Hochstrasser et al with either Alpenfels et al. or Lau et al. is not appropriate and in any event the cited art in combination does not render the claims obvious. Applicant requests that this rejection be withdrawn.

Claims 1-9 are rejected as being obvious over the combination of Alpenfels et al. with Saunders et al. or Flesher et al.

Here the examiner recognizes that Alpenfels et al. does not involve the inclusion of any compound that is an oxygen scavenger, and proposes to combine this reference with the latter two. However, this combination is not appropriate.

The process of Alpenfels et al., taken as a whole, is designed for the purpose of producing cross-linked polyacrylamide electrophoresis gels for separation of materials such as proteins. The examples show use of ammonium persulfate (APS) with TEMED as a polymerization catalyst.

Saunders et al., on the other hand, disclose a process for producing linear polymers of polyacrylamide in which the amount of cross-linking is kept to a minimum (col. 1 lines 8-9). Cross-linking is said to be undesirable because such products are water-insoluble (col. 1 lines 51-54). The Saunders et al. products must be water-soluble; they are used not for electrophoresis but as flocculants for suspended solids in water and strengthening agents for paper. Typically such polymers had been produced using a redox catalyst combination such as a sulfite with an oxidizing salt. However, a delicate balance had to be struck between using a greater amount of the sulfite, which can produce a positive result of essentially eliminating toxic monomeric acrylamide but can produce a polymer of too low a molecular weight, and using too little sulfite, which produces a suitable polymer but one that has too high a content of toxic monomer.

Saunders et al. discovered that a much smaller amount of sulfite could be used in the catalyst while still producing a polymer with a very low amount of monomer because the other component of the redox catalyst, an oxidizing salt such as a persulfate, could reduce monomer content in the resulting environment (col. 3 lines 1-8). The examiner takes the position that it would be obvious to combine the two disclosures because the use of the redox polymerization catalysts involves basic polymerization chemistry, irrespective of the end use of the products.

However, Applicant submits that while both references involve acrylamide polymerization, the issue of whether they may be combined cannot be reduced to one of "basic polymerization chemistry". The two patents produce different products - one (Alpenfels et al.) is aimed at producing a cross-linked polymer (and includes a cross-linking agent), the other (Saunders et al.) at producing a linear polymer with as little cross-linking as possible. The products have totally different properties and are aimed at totally different uses. The inclusion of a persulfate in the Saunders et al. work is to produce a polyacrylamide containing as little as possible of the monomeric compound, which is toxic. Alpenfels et al., on the other hand, are concerned entirely with the provision of certain structural features in electrophoresis gel equipment. The process disclosed in Alpenfels et al. is simply there as an example of a standard PAGE gel production process. There is no interest in Alpenfels for any type of process improvement, and no reason to add any sulfite, least of all certain amounts as shown in Saunders et al. Those skilled in the art of producing polyacrylamide gels would not look to Alpenfels et al. for any significant process information, and would not look to Saunders et al. for any useful information in connection with development of an electrophoresis gel process.

Flesher et al., like Saunders et al., disclose a process for the production of linear polyacrylamides, for similar use as flocculants. Viscosifying acidic electroplating fluids, descaling fluids and rust inhibitor solutions, as well as flocculants in general, are among the desired uses (col. 6 lines 7-24). The work of Flesher et al. is aimed at providing improved polyacrylamide flocculating agents that can be used in place of other

such agents. Here again, cross-linking is undesirable (col. 2 lines 31-57). These polymers must be cationic for the intended uses (col. 3 lines 52-55), and are made so by the inclusion of a quaternary amine salt or a tertiary amine.

Flesher et al. contain no discussion of catalysts to be used in producing such polymers. The only mention of any catalysts is in the examples, and no reason is given why they were chosen or what if any advantage they provide. Thus, the cited portion of Flesher et al., at col. 8 lines 14-16, states that the polymerization catalyst was a mixture of potassium bromate, sodium sulfite, and 4,4'-azobis-4-cyano-valeric acid. In Example 5, a combination of t-butyl hydroperoxide and sodium metabisulfite is used.

As with Saunders et al., those skilled in the art would not look to this reference for any information useful in modifying the skimpy process information in Alpenfels et al., and would have no reason to substitute these redox catalysts for the ammonium persulfate/TEMED of Alpenfels et al.

In fact, combining Flesher et al. with Alpenfels would be considered undesirable by those skilled in the art. Flesher et al. (col. 2 lines 50-57) advises conducting the reaction in the presence of a mercaptan to hold down the molecular weight of the polymer to a certain extent. The mercaptan used in the examples is 2-mercaptoethanol (Examples 5 and 6). However, as discussed below, it is well known in the art that the presence of 2-mercaptoethanol is deleterious to gel formation, and that this compound should not be present during gel formation. This item highlights the differences between the gel formation process of Alpenfels et al. (and the claimed process) and the linear polymer-flocculant process of Flesher et al.

Of the three references, only Alpenfels et al. discloses any information about prevention of oxygen from entering the polyacrylamide, and that reference discloses the use of an oxygen barrier coating. Nothing in the secondary references would cause one skilled in the art to substitute the redox catalysts of them for the catalyst of Alpenfels et al., and nothing would indicate that using an oxygen scavenger as claimed could obviate the need for the Alpenfels et al. oxygen barrier.

Withdrawal of this rejection is respectfully requested.

Finally, claims 1-13 are rejected as obvious over a combination of Ogawa et al. with the other references. Ogawa et al. disclose improved polyacrylamide gels for use in electrophoresis. The reference (col. 1 line 62- col. 2 line 8) discloses that the polymerization can be inhibited by oxygen, so the gel formation must be carried out in the absence of oxygen. Ogawa et al. therefore teaches sealing the gel-forming solution from oxygen. This is sufficient, since Ogawa et al. use glass plates. However, the reference is relied on for the teaching at col. 13 lines 35-40:

"*The gel membrane of the invention may contain an oxidation inhibitor. The oxidation inhibitor can be chosen from various compounds heretofore known as oxidation inhibitors employable for the gel membrane for electrophoresis. Examples of the oxidation inhibitor include 1,4-dithiothreitol and 2-mercaptoethanol.*"

As can be seen from the above quotation, the reference mentions "oxidation inhibitors" that are not within the scope of the claimed invention. Indeed, these inhibitors are not equivalent to those claimed oxygen scavengers.

The reference does not state that these oxygen inhibitors are present during the gel formation process and, in fact, as known in the art, they normally would not be so employed.

The examiner is referred to the sections of the Andrews and Hames texts submitted in the accompanying Information Disclosure Statement. The two compounds mentioned in Ogawa et al. as oxygen inhibitors, dithiothreitol and 2-mercaptoethanol, are used not to ward off deleterious effects of oxygen on a gel but to inhibit the formation of an oxidizing atmosphere in the gel during electrophoresis, so as to inhibit possible oxidation of proteins. As such, they are usually added to the sample that is subjected to electrophoresis. Both compounds are known to inhibit polymerization or gelling so that their presence during gel formation is undesirable or deleterious. See Andrews et al., p. 88 first full paragraph and Hames et al. in the passage beginning at the bottom of p. 32 and continuing to p. 36.

Those skilled in the art would thus understand Ogawa et al. to be referring to inhibition of oxygen during electrophoresis so as to avoid oxidation of proteins in the sample, and not to the use of such compounds at the time of gel formation.

The other references are not combinable with this disclosure of Ogawa et al. Alpenfels et al. disclose an oxygen barrier. Hochstrasser et al. disclose a compound that should be used and compounds that should not be used, both types of which are usable in Applicant's process. The other references do not add to these disclosures, as discussed above.

CONCLUSION

In view of the foregoing, Applicant submits that the claims in this application are allowable over the cited art.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned.

Respectfully submitted,

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